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Cumulative ultraviolet radiation flux in adulthood and risk of incident skin cancers in women

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Background: Solar ultraviolet (UV) exposure estimated based on residential history has been used as a sun exposure indicator in previous case–control and descriptive studies. However, the associations of cumulative UV exposure based on residential history with different skin cancers, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), have not been evaluated simultaneously in prospective studies.

Methods: We conducted a cohort study among 108 578 women in the Nurses' Health Study (1976–2006) to evaluate the relative risks of skin cancers with cumulative UV flux based on residential history in adulthood.

Results: Risk of SCC and BCC was significantly lower for women in lower quintiles *vs* the highest quintile of cumulative UV flux (both P for trend <0.0001). The association between cumulative UV flux and risk of melanoma did not reach statistical significance. However, risk of melanoma appeared to be lower among women in lower quintiles *vs* the highest quintile of cumulative UV flux in lag analyses with 2–10 years between exposure and outcome. The multivariable-adjusted hazard ratios per 200×10^{-4} Robertson–Berger units increase in cumulative UV flux were 0.979 (95% confidence interval (CI): 0.933, 1.028) for melanoma, 1.072 (95% CI: 1.041, 1.103) for SCC, and 1.043 (95% CI: 1.034, 1.052) for BCC.

Conclusions: Associations with cumulative UV exposure in adulthood among women differed for melanoma, SCC, and BCC, suggesting a potential variable role of UV radiation in adulthood in the carcinogenesis of the three major skin cancers.

Ultraviolet (UV) radiation and geographic location previously have been implicated as risk factors for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma (Bulliard, 2000; Almahroos and Kurban, 2004; Qureshi *et al*, 2008). Populations living in geographic locations with latitudes closer to the equator have been reported to have higher rates of BCC and SCC than that in other populations (Suzuki *et al*, 1996; Leiter and Garbe, 2008). The incidence ratios of BCC:SCC vary by latitude from 3 : 1 to 10 : 1 (Urbach, 1991). However, SCC appears to be more strongly associated with UV exposure than BCC (Magnus, 1991; Urbach, 1991; English *et al*, 1998; Ramos *et al*, 2004); and subjects who receive high UV doses are more likely to develop SCC and have a lower BCC:SCC ratio when compared with those who receive lower UV doses (Ramos *et al*, 2004). Although there is sufficient evidence suggesting that the spectrum of UV radiation reaching the Earth's surface is involved in the development of melanoma (IARC, 2006), the association between sun exposure and melanoma is very different from that between sun exposure and

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BCC and SCC (Kennedy *et al*, 2003). Compared with SCC and BCC, melanoma is more likely to be associated with a pattern of intermittent sun exposure rather than continuous sun exposure (Gandini *et al*, 2005; Landi *et al*, 2006). For example, a meta-analysis using data from 57 original case–control, cohort or cross-sectional studies supports the hypothesis that there is a positive association for intermittent sun exposure and an inverse association for a highly continuous pattern of sun exposure with regard to melanoma risk (Gandini *et al*, 2005). In contrast, non-melanoma skin cancer, especially SCC, is less likely to be associated with an intermittent pattern of sun exposure (English *et al*, 1998; Leiter and Garbe, 2008).

Exposure to sunlight, often ascertained by survey questions such as 'time spent outdoors' at various ages, has traditionally been used in case–control studies (English *et al*, 1998; Kennedy *et al*, 2003; Iannacone *et al*, 2012). However, it may be subject to recall bias and misclassification bias. In addition, these measures only account for duration of exposure and do not account for intensity of exposure. As a result, it is difficult to quantify sun exposure using 'time spent outdoors' or similar measures. Other methods (e.g., UV exposure based on residential history) to capture sun exposure have been developed (Fears *et al*, 2002).

Assessments on UV exposure based on residential history have been used in several previous case–control or descriptive studies to estimate the association between UV exposure and melanoma (Jemal *et al*, 2000; Fears *et al*, 2002; Tatalovich *et al*, 2006). One such measure is the UV index, which is developed by the National Weather Service and the Environmental Protection Agency, to predict UV radiation levels on a scale of 0 to >11 (Coldiron, 1998; Schmalwieser *et al*, 2005). This measure accounts for latitude, altitude, cloud cover, haze, time of day, and ozone concentrations (Blunden *et al*, 2004; Brooks *et al*, 2005). In our recent study using data from the Nurses' Health Study (NHS) with adjustment for host risk factors, the relative risk of SCC was significantly higher among women who resided in states with medium and high UV indices when compared with women who resided in states with low UV index in early life (birth, ages 15 and 30) (Qureshi *et al*, 2008). In contrast, the relative risk of BCC was lower than that of SCC, whereas the relative risk of melanoma was not significantly different across the gradient of UV indices ($\leqslant 5$, 6, and $\geqslant 7$) (Qureshi *et al*, 2008). However, this study only assessed the associations of skin cancers with sun exposure intensity at three specific time points (at birth, ages 15 and 30) in early life, and did not assess the associations of skin cancers with sustained UV exposure over long durations.

Another surrogate measure to assess cumulative sun exposure that is less influenced by recall bias is UV radiation flux (Scotto *et al*, 1988, 1996; Jemal *et al*, 2000; Fears *et al*, 2002; Tatalovich *et al*, 2006). Based on residential histories, UV flux is calculated where UV flux units represent radiant energy per unit area and are measured in Robertson–Berger (RB) metre units (Fears *et al*, 2002). The United States has been considered an ideal model to study the effect of geography on the risk of incident skin cancer given the variation in both UV indices and UV flux across a north–south gradient (Scotto and Fears, 1987; Jemal *et al*, 2000).

Although data on melanoma are collected in the Surveillance Epidemiology and End Results (SEER) database, no US national registries track either BCC or SCC (Elder, 1995; Boni *et al*, 2002). For this reason, data on all three types of skin cancers within the same population are difficult to obtain. In this study, we characterise the association between cumulative sun exposure over long durations in adulthood and risks of incident melanoma, SCC, and BCC in the same cohort (NHS) of US women as studied by Qureshi *et al* (2008). We use cumulative UV flux during the cohort follow-up as a surrogate marker for cumulative sun exposure in adulthood.

MATERIALS AND METHODS

Study population. The NHS is an ongoing prospective cohort study that was established in 1976 when 121 700 female registered nurses completed a mailed questionnaire that included items about risk factors for chronic diseases (Colditz *et al*, 1986). At enrolment, study participants were 30–55 years of age and resided in the following 11 states: California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas. These states were originally chosen based on their size and approval of the study by the respective nursing associations. Since cohort inception, participants now reside in every US state. The cohort has a high follow-up rate up to 96% (Giovannucci *et al*, 1995). Institutional human studies research approval was obtained at the Brigham and Women's Hospital. The completion and return of the self-administered questionnaire was considered as informed consent.

Case ascertainment. NHS participants have been asked to report new diagnoses of melanoma (International Classification of Diseases for Oncology third revision (ICD-O-3) code: M8720/3)], SCC (ICD-O-3 code: M8070/3), and BCC (ICD-O-3 code: M8090/3) during the follow-up. Women who reported melanoma or SCC were asked for permission to obtain medical records, which were reviewed by study physicians to confirm melanoma and SCC diagnoses. The confirmation rates for melanoma and SCC reached 93% and 97%, respectively. SCC *in situ* and melanoma *in situ* were excluded from this analysis. Medical records were not obtained for self-report of BCC. However, a high accuracy of self-reported BCC over 90% has been demonstrated in previous validation studies (Colditz *et al*, 1986; Hunter *et al*, 1992).

Estimation of cumulative UV flux. UV flux is an estimate of the amount of UVB radiation (wavelength range 290–315 nm) and part of UVA radiation (wavelength range 315–330 nm) reaching the earth's surface that is measured by RB metres (Scotto *et al*, 1988). UV flux takes into account factors that could affect this parameter, such as cloud cover, altitude, and latitude (Scotto *et al*, 1996). Radiation in the 290–330-nm wavelength range is monitored by a magnesium tungstate sensor and weighted according to an action spectrum that parallels that for skin erythema (Scotto *et al*, 1988). The RB metre integrates the amounts of UV radiation and provides counts in 'sunburn units' (RB units) (Scotto *et al*, 1988, 1996). The measured UV flux could have varied according to geographic factors, such as latitude, longitude, and altitude, and physical, or meteorological factors (Scotto *et al*, 1988). A map showing the gradient of annual UV radiation in RB units across the United States could be found elsewhere (Jemal *et al*, 2000). An amount of 440 RB units may produce a typical sunburn reaction to untanned Caucasian skin (Scotto *et al*, 1996). This amount of biologically effective radiation (relative to a wavelength of 297 nm) is referred to as the minimal erythema dose and is equivalent to ~ 25–$35\ \mathrm{mJ\,cm^{-2}}$ (DeLuisi and Harris, 1983).

UV flux for each study participant was estimated based on residential history according to detailed methods documented previously (Fears *et al*, 2002). Briefly, the potential cumulative UV flux that a participant could have received over a period of time was estimated by summing the annual UV flux data over the follow-up (Scotto *et al*, 1996; Fears *et al*, 2002). In the present study, residential locations were available for 1976 and 1986–2006 for cohort participants. If the woman lived in the same residence in 1976 as in 1986, we assumed that she lived in the same residence during this period. If the residences in 1976 and 1986 were different, we assumed that in 1978–1980 she lived in the residence as in 1976, and in 1982–1984 she lived in the residence as in 1986 (Arkema *et al*, 2013). Place of residence during a 2-year

cycle for each participant was rounded off to the biennial July of each even numbered cycle year. If a participant moved during the cycle, we assumed that she spent the entire cycle (2-year period) at the residence that she indicated at the end of the cycle.

Statistical analysis. The analysis was restricted to Caucasian women who did not have missing data on residence in 1976. Participants contributed person-time from the date of return of the 1976 questionnaire. Accumulation of follow-up time ceased upon the date of the first diagnosis of a cancer, death, or return of the 2006 questionnaire, whichever came first. Women with a baseline history of any cancer before 1976 were excluded from the analysis. We used Cox proportional hazards models stratified by age (categorised in 5-year increments) and follow-up intervals to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident skin cancers associated with cumulative UV flux. Cumulative UV flux was modelled as a residence and time-varying variable divided into quintiles, and trend tests were performed by assigning median values for these quintiles and treating the new variable as a continuous term in the models. Women in the highest quintile were set as the reference group. For multivariable analyses, covariates relevant to skin cancer risk were included in the models, specifically mole counts on left arm (none, 1–2, 3–5, or $\geqslant 6$); hair colour at age 20 years (black, dark brown, light brown, blonde, or red); ability to tan (almost none, little tan, average tan, or deep tan); susceptibility to burn (no burn, some redness, burn, painful burn, or painful burn with blisters); lifetime severe sunburn counts (none, 1–2, 3–5, or $\geqslant 6$); family history of melanoma (yes or no) (Qureshi *et al*, 2011); UV indices at state of residence at birth, 15 and 30 years of age (<5, 6, and $\geqslant 7$) (Qureshi *et al*, 2008); physical activity level (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, and $\geqslant 27.0$ metabolic equivalents hours per week) (Lee *et al*, 2009); and rotating night shift (never, 1–9 years, and $\geqslant 10$ years) (Schernhammer *et al*, 2011). In addition, we fitted adjusted Cox proportional hazards models with cumulative UV flux using restricted cubic splines to examine the shapes of the dose–response relationships between cumulative UV flux and risk of skin cancers (Durrleman and Simon, 1989). Multivariable HRs were estimated for cumulative UV flux levels ranging from 200 to 5400×10^{-4} RB units relative to a reference value of 1680×10^{-4} RB units. Modelling results are shown as graphs of the smoothed splines with 95% CIs.

Sensitivity analyses were conducted using lag times of 2–10 years between exposure and outcome. For example, incident skin cancers during the 1998–2000 cycle would be matched to cumulative UV flux in 1996 for 2-year lag analysis and matched to cumulative UV flux in 1988 for 10-year lag analysis. In these sensitivity analyses (i.e., lag analyses), the quintile cut points for cumulative UV flux may be different from those used in the main analyses because of different follow-up years. All data analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA), and all *P*-values are two-sided with $P \leqslant 0.05$ considered as statistically significant.

RESULTS

During $\sim$2.5 million person-years of follow-up time, 634 first diagnoses of melanoma and 1065 first diagnoses of SCC were confirmed, and 15 159 first diagnoses of BCC were reported among 108 578 women. The distribution of cumulative UV flux was similar across different categories of most of the inherent skin cancer risk factors, whereas cumulative UV flux was higher among participants living in areas with high UV indices ($\geqslant 7$) in early life and among participants with rigorous physical activity (Table 1). The incidence of different skin cancers was variable across quintiles of cumulative UV flux (Table 2). The trend of increasing incidence of skin cancer with increasing UV flux was most apparent for SCC (1% cases in the lowest quintile *vs* 52% cases in the highest quintile) as compared with that for BCC (1% cases in the lowest quintile *vs* 34% cases in the highest quintile) or melanoma (14% cases in the lowest quintile *vs* 27% cases in the highest quintile).

There was little difference between the age-adjusted HRs and multivariable HRs for skin cancers associated with quintiles of cumulative UV flux (Table 2). Compared with women in the highest quintile, the HRs for melanoma were not statistically significant for women in lower quintiles (P for trend $= 0.77$). However, the trend in HRs from the highest quintile to the lowest quintile was statistically significant for both SCC and BCC (P for trend < 0.0001). Results from cubic spline regression suggest that SCC appeared to be most strongly associated with increasing cumulative UV flux when compared with melanoma or BCC (Supplementary Figure S1). Analyses using cumulative UV flux as a continuous variable further suggest a more apparent increasing trend of SCC risk associated with cumulative UV flux (Table 2). The multivariable HRs per 200×10^{-4} RB units increase in cumulative UV flux were 0.979 (95% CI: 0.933, 1.028) for melanoma, 1.072 (95% CI: 1.041, 1.103) for SCC, and 1.043 (95% CI: 1.034, 1.052) for BCC. We explored the possible latent periods of exposure of 2–10 years, and found that the associations for different skin cancers with cumulative UV flux were generally consistent with the primary analyses (Table 3).

DISCUSSION

In the prospective cohort study of women residing across the United States, we demonstrated different associations of melanoma, SCC, and BCC with long-term UV exposure in adulthood, as measured by cumulative UV flux, a measure based on residential history. Our findings suggest that risk of SCC is more strongly associated with cumulative UV flux in adulthood than risks of BCC and melanoma. These results are unchanged after adjustment for a number of known skin cancer risk factors.

That sun exposure and geographic location are risk factors for the three most common types of skin cancer is well known; however, the nature of this relationship is most clearly established for BCC and SCC. This association is less clear in the case of melanoma, and evidence from case–control and descriptive studies both supports and refutes the association between geographic location/sun exposure and melanoma risk. For example, the absolute change in melanoma mortality for a 10% increase in UVB radiation among females in the United States decreased from 0.08 additional deaths per 100 000 person-years in 1950–1959 to 0.01 additional deaths in 1990–1995 (Jemal *et al*, 2000). Another case–control study with 966 individuals found that lifetime sun exposure (assessed by total sun exposure hours using a Residence Work Calendar) was predominantly associated with an increased risk of SCC but a lower risk of melanoma (Kennedy *et al*, 2003). On the other hand, in an Australian study involving over 1000 melanoma cases based on population-based cancer registries in three states, the authors found that a decrease in latitude (related to an increase in sun exposure intensity) was associated with an increased incidence of melanoma (Green *et al*, 1996). Similar results on increased incident melanoma in geographic regions with decreased latitude have been reported among whites in a study using 43 population-based cancer registries in North America and Europe (Crombie, 1979) and in another study using 11 cancer registries in the United States (Eide and Weinstock, 2005). Evidence from a recent study using data from two independent case–control groups with a total of 197 melanoma cases also suggests that melanomas without signs of chronic sun-induced damage are more likely to occur on intermittently exposed body sites (e.g., trunk) rather than continuously exposed body sites

Table 1. Distribution of cumulative UV flux ($\times 10^{-4}$ RB units) according to skin cancer risk factors

	No. of participants (%)	Mean ± s.d.	Range
Ability to tan after 2 h of sun exposure as a child			
Almost none	7179 (9)	1643 ± 1016	200–5362
Little tan	18 570 (22)	1652 ± 1010	200–5392
Average tan	37 715 (46)	1676 ± 1021	200–5340
Deep tan	19 383 (23)	1692 ± 1031	200–5370
Skin reaction after 2 h of sun exposure during childhood			
No burn	16 263 (19)	1692 ± 1026	200–5362
Some redness	36 456 (44)	1679 ± 1023	200–5370
Burn	18 671 (22)	1651 ± 1010	200–5392
Painful burn	7981 (10)	1658 ± 1019	200–5296
Painful burn with blisters	4425 (5)	1647 ± 1032	200–5200
Natural hair colour at age 20			
Red	3519 (4)	1638 ± 1021	200–5130
Blonde	9792 (12)	1672 ± 1034	200–5392
Light brown	32 401 (39)	1672 ± 1021	200–5362
Dark brown	35 480 (42)	1673 ± 1017	200–5362
Black	2557 (3)	1689 ± 1036	200–5370
Moles count on the left arm			
None	46 214 (63)	1683 ± 1025	200–5370
1–2	23 781 (32)	1669 ± 1020	200–5328
3–5	1959 (3)	1626 ± 997	200–5040
⩾6	1488 (2)	1641 ± 1018	200–5296
Lifetime severe sunburn counts			
None	48 293 (63)	1674 ± 1020	200–5392
1–2	16 310 (21)	1670 ± 1019	200–5296
3–5	6309 (8)	1678 ± 1027	200–5182
⩾6	5788 (8)	1654 ± 1023	200–5296
Family history of melanoma			
No	101 972 (94)	1682 ± 1030	200–5392
Yes	6606 (6)	1664 ± 1014	200–5362
UV index at state of residence at birth			
⩽5	24 892 (33)	1636 ± 970	200–5296
6	42 088 (56)	1626 ± 973	200–5362
⩾7	7879 (11)	2098 ± 1272	200–5370
UV index at state of residence at age 15			
⩽5	24 722 (33)	1630 ± 965	200–5296
6	42 311 (56)	1616 ± 964	200–5362
⩾7	7917 (11)	2144 ± 1288	200–5370
UV index at state of residence at age 30			
⩽5	20 603 (28)	1579 ± 919	200–5296
6	41 942 (57)	1575 ± 923	200–5296
⩾7	10 762 (15)	2163 ± 1284	200–5370
Physical activity level			
<3.0 Metabolic equivalents hours per week	20 845 (28)	1624 ± 1032	200–5296
3.0–8.9 Metabolic equivalents hours per week	20 032 (27)	1643 ± 1007	200–5362
9.0–17.9 Metabolic equivalents hours per week	14 393 (19)	1743 ± 1025	200–5296
18.0–26.9 Metabolic equivalents hours per week	7919 (11)	1791 ± 1023	200–5296
⩾27.0 Metabolic equivalents hours per week	11 375 (15)	1869 ± 1032	200–5392
Rotating night shift			
Never	30 775 (41)	1686 ± 1026	200–5296
1–9 Years	36 222 (48)	1676 ± 1020	200–5362
⩾10 Years	9048 (12)	1659 ± 1011	200–5296

Abbreviations: RB = Robertson–Berger; UV = ultraviolet.

Table 2. Hazard ratios for melanoma, squamous cell carcinoma, and basal cell carcinoma according to cumulative UV flux

	No. of cases (%)	Age-adjusted HR (95%CI)	Multivariable HR (95%CI)[a]
Melanoma ($n = 634$ cases)			
UV flux Q1[b]	88 (14)	0.66 (0.30, 1.47)	0.85 (0.36, 2.01)
UV flux Q2	130 (21)	1.07 (0.58, 1.96)	1.32 (0.68, 2.55)
UV flux Q3	112 (18)	0.89 (0.56, 1.41)	1.02 (0.63, 1.67)
UV flux Q4	129 (20)	1.01 (0.74, 1.38)	1.07 (0.78, 1.47)
UV flux Q5	175 (28)	1.00	1.00
P for trend	—	0.68	0.77
Per 200×10^{-4} RB units increase[c]	—	1.004 (0.966, 1.044)	0.979 (0.933, 1.028)
Squamous cell carcinoma ($n = 1065$ cases)			
UV flux Q1[b]	7 (1)	0.04 (0.01, 0.29)	0.05 (0.01, 0.35)
UV flux Q2	69 (6)	0.29 (0.17, 0.48)	0.34 (0.20, 0.59)
UV flux Q3	162 (15)	0.51 (0.37, 0.69)	0.57 (0.40, 0.79)
UV flux Q4	272 (26)	0.70 (0.57, 0.85)	0.74 (0.60, 0.91)
UV flux Q5	555 (52)	1.00	1.00
P for trend	—	<0.0001	<0.0001
Per 200×10^{-4} RB units increase[c]	—	1.069 (1.046, 1.092)	1.072 (1.041, 1.103)
Basal cell carcinoma ($n = 15\,159$ cases)			
UV flux Q1[b]	152 (1)	0.41 (0.33, 0.52)	0.47 (0.37, 0.59)
UV flux Q2	2640 (17)	0.40 (0.36, 0.44)	0.45 (0.40, 0.51)
UV flux Q3	3505 (23)	0.59 (0.54, 0.64)	0.64 (0.58, 0.70)
UV flux Q4	3819 (25)	0.81 (0.76, 0.85)	0.84 (0.79, 0.89)
UV flux Q5	5043 (33)	1.00	1.00
P for trend	—	<0.0001	<0.0001
Per 200×10^{-4} RB units increase[c]	—	1.052 (1.045, 1.059)	1.043 (1.034, 1.052)

Abbreviations: CI = confidence interval; HR = hazard ratio; UV = ultraviolet.
[a]Multivariable analyses adjusted for age, susceptibility to burn, ability to tan, natural hair colour at age 20, number of moles on left arm, family history of melanoma, severe sunburn counts, UV indices at state of residence at birth, 15 and 30 years of age, physical activity level, and rotating night shift.
[b]UV flux quintiles: Q1 = 200–656, Q2 = 678–1294, Q3 = 1296–1872, Q4 = 1874–2614, and Q5 = 2616–5392×10^{-4} RB units, respectively.
[c]Cumulative UV flux was modelled as a continuous variable in the models.

(e.g., face) (Landi *et al*, 2006). Another meta-analysis using data from 57 original case–control, cohort, or cross-sectional studies also supports the hypothesis that there is a positive association for intermittent sun exposure and an inverse association for a highly continuous pattern of sun exposure with regard to melanoma risk (Gandini *et al*, 2005). Overall, these findings support the hypothesis that melanoma is associated with intermittent UV exposure rather than cumulative UV exposure. If this is correct, it may explain why we did not observe clear or consistent evidence of a positive association between melanoma and cumulative UV flux in our study population.

A major strength of this study is the ability to simultaneously evaluate the risks of BCC, SCC, and melanoma in the same cohort of women. The NHS provides an excellent opportunity to study a population across the United States with high rates of follow-up. In addition, we were able to adjust for a number of other skin cancer risk factors, including sun exposure-related behaviours (i.e., physical activity level and rotating night shift) based on detailed follow-up information.

One limitation of this study is the generalisability of these results to other populations in the United States, including men. Previous studies have reported evidence suggesting heterogeneous effects of sun exposure for men and women. In a previous case–control study with 176 skin cancer cases and 216 controls, lifetime sun exposure (derived by summing the total hours spent outdoors at work, sports, recreation, or yard work in direct sunlight) was more strongly associated with SCC risk in women, whereas early-age (age 15–24) sun exposure was more relevant to SCC risk in men (Chen *et al*, 2010). Another case–control study with 718 melanoma cases and 945 controls also found a stronger association of melanoma risk with increasing UV flux in men than that in women (Fears *et al*, 2002). Also the north–south gradient in melanoma risk has been demonstrated to be more apparent for men than that for women in New Zealand (Bulliard *et al*, 1994; Bulliard, 2000). Further studies are needed to clarify whether the observed associations between cumulative UV flux and three types of skin cancer exist for men.

A potential limitation of using UV flux levels measured in RB metres includes the fact that these measurements are estimates of real values of UV irradiation and do not take into account variables such as the amount of time spent in the sun and use of sunscreens or clothing. Therefore, the exposure may be subject to measurement error and misclassified; although, such misclassification is likely to be non-differential and attenuate the risk estimates. In addition, there is no significant interaction between cumulative UV flux and individual behaviours (i.e., physical activity level and rotating night shift) related to sun exposure, and analyses stratified by sun exposure-related behaviours revealed little difference in associations of cumulative UV flux with risk of skin cancers across different behaviour categories (data available upon request). These results suggest that cumulative UV flux based on residential history may be used as a relatively reliable surrogate of UV exposure over long durations. Another issue is that RB metres are temperature sensitive (Johnsen and Moan, 1991). However, the overall influence of temperature on RB counts is relatively small as demonstrated in a previous study, which found that the difference in average summer temperatures for Oslo city in the period from 1951 to 1989 would influence annual RB counts in a similar manner as an about 2% change in the total amount of atmospheric ozone (Johnsen and Moan, 1991). Finally, cumulative UV flux in adulthood does not account for sun exposure in early life, a period when exposure may also be important for associated skin cancer risk in adulthood (Whiteman *et al*, 2001; Iannacone *et al*, 2012). Although we adjusted for several potential confounders related to early-life sun exposure (i.e., UV indices at state of residence at birth, 15 and 30 years of age) in the multivariable analyses, our results may still need to be interpreted with caution.

In summary, we evaluated the associations of long-term UV exposure and risk of three types of skin cancer in a cohort of women in the United States, and found differences in risks of different skin cancers associated with cumulative UV flux over long durations in adulthood, a measure that was estimated taking residential history into account. We found that the risk of incident SCC was positively associated with cumulative UV flux in adulthood. A similar but less pronounced trend was seen for BCC. In contrast, incident melanoma risk was not significantly associated with cumulative UV flux. These dose–response relations remained the same after adjusting for other skin cancer risk factors. Previous findings from this cohort suggest that sun exposure intensity in early life may increase the risk of skin cancer in adulthood (Qureshi *et al*, 2008). Results from the present study provide further evidence that the quantity of sun exposure received over long durations in adulthood as indicated by cumulative UV flux may also increase the risk of skin cancer, particularly for SCC. The differences in risks of incident SCC, BCC, and melanoma as related to UV exposure history suggest a variable role of UV

Table 3. Multivariable hazard ratios[a] for melanoma, squamous cell carcinoma, and basal cell carcinoma with lags of 2–10 years between exposure and outcome

	2- year lag[b]		4- year lag[c]		6-year lag[d]		8-year lag[e]		10-year lag[f]	
	No. of cases	Multivariable HR (95% CI)	No. of cases	Multivariable HR (95% CI)	No. of cases	Multivariable HR (95% CI)	No. of cases	Multivariable HR (95% CI)	No. of cases	Multivariable HR (95% CI)
Melanoma										
UV flux Q1	95	0.47 (0.19, 1.19)	99	0.96 (0.38, 2.42)	81	0.62 (0.19, 2.04)	84	0.50 (0.16, 1.55)	72	0.93 (0.33, 2.59)
UV flux Q2	110	0.64 (0.30, 1.34)	102	0.97 (0.47, 1.99)	96	0.83 (0.36, 1.96)	78	0.62 (0.27, 1.45)	65	0.66 (0.29, 1.50)
UV flux Q3	101	0.68 (0.41, 1.15)	84	0.84 (0.48, 1.46)	76	0.76 (0.43, 1.36)	66	0.72 (0.39, 1.34)	62	0.81 (0.45, 1.43)
UV flux Q4	122	0.91 (0.66, 1.25)	132	0.92 (0.66, 1.30)	120	0.91 (0.63, 1.30)	115	0.82 (0.58, 1.18)	109	0.90 (0.62, 1.30)
UV flux Q5	167	1.00	139	1.00	131	1.00	119	1.00	106	1.00
P for trend		0.14		0.74		0.40		0.19		0.61
Squamous cell carcinoma										
UV flux Q1	13	0.12 (0.05, 0.31)	44	0.51 (0.23, 1.12)	66	0.57 (0.21, 1.55)	83	0.22 (0.10, 0.49)	88	0.62 (0.30, 1.29)
UV flux Q2	91	0.34 (0.20, 0.59)	102	0.51 (0.30, 0.87)	112	0.60 (0.33, 1.07)	114	0.43 (0.25, 0.75)	119	0.57 (0.35, 0.92)
UV flux Q3	174	0.64 (0.45, 0.90)	165	0.67 (0.47, 0.94)	174	0.72 (0.51, 1.01)	168	0.40 (0.40, 0.82)	165	0.73 (0.52, 1.03)
UV flux Q4	264	0.78 (0.63, 0.96)	287	0.87 (0.70, 1.09)	257	0.87 (0.69, 1.09)	248	0.72 (0.58, 0.89)	230	0.76 (0.60, 0.95)
UV flux Q5	518	1.00	460	1.00	440	1.00	407	1.00	373	1.00
P for trend		0.0004		0.02		0.05		0.0002		0.01
Basal cell carcinoma										
UV flux Q1	885	0.50 (0.42, 0.60)	1921	0.42 (0.35, 0.49)	2650	0.36 (0.29, 0.44)	2204	0.39 (0.32, 0.48)	1743	0.65 (0.54, 0.78)
UV flux Q2	2882	0.57 (0.50, 0.66)	2761	0.55 (0.48, 0.63)	2457	0.53 (0.46, 0.61)	2295	0.59 (0.51, 0.68)	2311	0.82 (0.71, 0.94)
UV flux Q3	3293	0.79 (0.72, 0.86)	2838	0.74 (0.67, 0.81)	2779	0.77 (0.70, 0.85)	2367	0.77 (0.69, 0.85)	2102	0.87 (0.79, 0.97)
UV flux Q4	3487	0.90 (0.85, 0.96)	3501	0.84 (0.79, 0.90)	2993	0.85 (0.80, 0.91)	2824	0.86 (0.80, 0.92)	2574	0.95 (0.88, 1.02)
UV flux Q5	4612	1.00	4137	1.00	3891	1.00	3472	1.00	3092	1.00
P for trend		<0.0001		<0.0001		<0.0001		<0.0001		0.0001

Abbreviations: CI = confidence interval; HR = hazard ratio; UV = ultraviolet.

[a]Multivariable analyses adjusted for age, susceptibility to burn, ability to tan, natural hair colour at age 20, number of moles on left arm, family history of melanoma, severe sunburn counts, UV indices at state of residence at birth, 15 and 30 years of age, physical activity level, and rotating night shift.

[b]UV flux quintiles for 2-year lag analysis: Q1 = 200–654, Q2 = 656–1130, Q3 = 1132–1800, Q4 = 1802–2484 and Q5 = 2486–5000 × 10^{-4} RB units, respectively.

[c]UV flux quintiles for 4-year lag analysis: Q1 = 200–624, Q2 = 648–1128, Q3 = 1130–1638, Q4 = 1640–2260 and Q5 = 2262–4608 × 10^{-4} RB units, respectively.

[d]UV flux quintiles for 6-year lag analysis: Q1 = 200–580, Q2 = 600–1038, Q3 = 1040–1526, Q4 = 1528–2072 and Q5 = 2074–4216 × 10^{-4} RB units, respectively.

[e]UV flux quintiles for 8-year lag analysis: Q1 = 200–452, Q2 = 468–904, Q3 = 906–1384, Q4 = 1386–1872 and Q5 = 1874–3824 × 10^{-4} RB units, respectively.

[f]UV flux quintiles for 10-year lag analysis: Q1 = 200–436, Q2 = 452–872, Q3 = 874–1306, Q4 = 1308–1742 and Q5 = 1744–3432 × 10^{-4} RB units, respectively.

radiation in the carcinogenesis of the three major skin cancers. Considering the multiple effects of UV radiation has in the cutaneous tissue, including DNA damage, immune-suppression, and vitamin D production (Norval *et al*, 2011), additional work is needed to improve our understanding of the role that UV radiation has in the pathophysiology of the three major types of skin cancer.

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